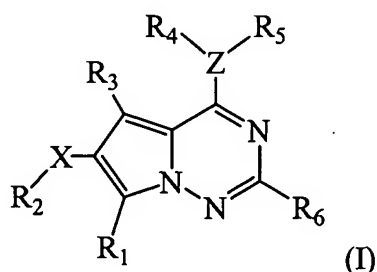


AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):



or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R₃ is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH₂;

X is selected from -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, ~~-CO₂-~~, -NR₁₀-,
-NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-, -NR₁₀SO₂NR₁₁-,
-SO₂NR₁₀-, -C(=O)NR₁₀-, halogen, nitro, and cyano, or X is absent;

Z is selected from O, S, N, and CR₂₀, wherein when Z is CR₂₀, said carbon atom may form an optionally-substituted bicyclic aryl or heteroaryl with R₄ and R₅;

R₁ is hydrogen, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂,
-SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₄R₂₅, -NR₂₁SO₂NR₂₄R₂₅,
-NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halogen, nitro, or
cyano;

R₂ is selected from:

- hydrogen, provided that R₂ is not hydrogen when X is -S(=O)-, -SO₂-, -NR₁₀CO₂-, or -NR₁₀SO₂-;
- alkyl, alkenyl, and alkynyl optionally substituted with up to four R₂₆ or pentafluoroalkyl;
- aryl and heteroaryl optionally substituted with up to three R₂₇; and

- d) heterocyclo and cycloalkyl optionally substituted with keto ($=O$), up to three R_{27} , and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
- e) R_2 is absent if X is halogen, nitro or cyano;
- (i) R_4 is substituted aryl, aryl substituted with $NHSO_2$ alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and
- R_5 is hydrogen, alkyl, or substituted alkyl, except when Z is O or S, R_5 is absent, or alternatively,
- (ii) R_4 and R_5 taken together with Z form an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl;
- R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;
- R_{10} and R_{11} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;
- R_7 , R_8 , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;
- R_{20} is hydrogen, lower alkyl, or substituted alkyl, or R_{20} may be absent if the carbon atom to which it is attached together with R_4 and R_5 is part of an unsaturated bicyclic aryl or heteroaryl;
- R_{22} is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;
- R_{26} is selected from halogen, trifluoromethyl, haloalkoxy, keto ($=O$), nitro, cyano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alkyl; aryl optionally substituted with one to three R_{27} ; cycloalkyl optionally substituted with keto ($=O$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocyclo optionally substituted with keto ($=O$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycle, or may be taken together to form a C_{3-7} heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy; and

R₂₇ is selected from alkyl, R₃₂, and C₁₋₄alkyl substituted with one to three R₃₂, wherein each R₃₂ group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, -SR₃₀, -OR₃₀, -NR₃₀R₃₁, -NR₃₀SO₂, -NR₃₀SO₂R₃₁, -SO₂R₃₀, -SO₂NR₃₀R₃₁, -CO₂R₃₀, -C(=O)R₃₀, -C(=O)NR₃₀R₃₁, -OC(=O)R₃₀, -OC(=O)NR₃₀R₃₁, -NR₃₀C(=O)R₃₁, -NR₃₀CO₂R₃₁, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R₃₀ and R₃₁ are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C₃₋₇cycloalkyl, and heterocycle, or may be taken together to form a C₃₋₇heterocycle.

2. (Currently Amended) The method of claim 1 comprising administering to the patient at least one compound having the formula (I), or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₃ is methyl, -CF₃, or -OCH₃;

X is selected from -C(=O)-, -~~CO₂~~, -NR₁₀-, -NR₁₀C(=O)-, -NR₁₀CO₂-, -NR₁₀SO₂-, -SO₂NR₁₀-, and -C(=O)NR₁₀-, or X is absent;

Z is N;

R₂ is hydrogen, C₂₋₆alkyl, C₁₋₄alkyl substituted with up to four R₂₆, pentafluoroalkyl, or aryl or heteroaryl optionally substituted with up to two R₂₇;

R₄ is phenyl substituted with one R₁₂ and zero to three R₁₃;

R₅ and R₁₀ independently are selected from hydrogen and lower alkyl;

R₁₂ is carbamyl, sulfonamido, arylsulfonylamine, or ureido, each of which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or alkylsulfonylamine;

R₁₃ at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, -OR₁₄, -C(=O)alkyl, -OC(=O)alkyl, -NR₁₅R₁₆, -SR₁₅, -NO₂, -CN, -CO₂R₁₅, -CONH₂, -SO₃H, -S(=O)alkyl, -S(=O)aryl, -NHSO₂-aryl-R₁₇, -NHSO₂-alkyl, -SO₂NHR₁₇, -CONHR₁₇, and -NHC(=O)NHR₁₇;

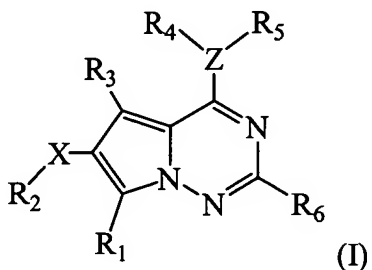
R₁₄ is hydrogen, alkyl, or aryl;

R₁₅ is hydrogen or alkyl;

R₁₆ is hydrogen, alkyl, aralkyl, or alkanoyl; and

R₁₇ is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl.

3. (Currently Amended) A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₃ is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH₂;

X is selected from -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, ~~-CO₂-~~, -NR₁₀-,
-NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-, -NR₁₀SO₂NR₁₁-,
-SO₂NR₁₀-, -C(=O)NR₁₀-, halogen, nitro, and cyano, or X is absent;

Z is O, S, N, or CR₂₀;

R₁ is hydrogen, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂,
-SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂,
-NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halogen, nitro, or cyano;

R₂ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,
aryl, substituted aryl, heterocyclo, substituted heterocyclo, aralkyl, substituted aralkyl, or
heterocycloalkyl, or substituted heterocycloalkyl, or when X is halo, nitro or cyano, R₂ is
absent, provided that R₂ is not hydrogen when X is -S(=O)-, -SO₂-, -NR₁₀CO₂-, or
-NR₁₀SO₂-;

R₄ is substituted aryl, aryl substituted with NHSO₂alkyl, substituted heteroaryl, or an optionally-
substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring
system;

R₅ is hydrogen, alkyl, or substituted alkyl, except that when Z is O or S, R₅ is absent;

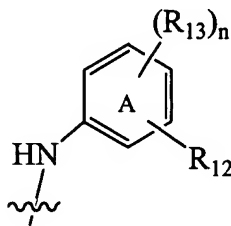
R₆ is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo,
-NR₇R₈, -OR₇, or halogen;

R₇, R₈, R₁₀, R₁₁, R₂₁, R₂₄, and R₂₅ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

R₂₀ is hydrogen, lower alkyl, or substituted alkyl; and

R₂₂ is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo.

4. (Currently Amended) The method of claim 3 comprising administering to the patient at least one compound of formula (I), in which R₄, R₅ and Z are represented by R₄ and R₅ taken together with Z form:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₁₂ is attached to any available carbon atom of phenyl ring A and is selected from carbamyl, sulfonamido, arylsulfonylamine, and ureido, each of which is optionally substituted with up to one of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or C₁₋₄alkylsulfonylamine;

R₁₃ is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, -OR₁₄, -C(=O)alkyl, -OC(=O)alkyl, -NR₁₅R₁₆, -SR₁₅, -NO₂, -CN, -CO₂R₁₅, -CONH₂, -SO₃H, -S(=O)alkyl, -S(=O)aryl, -NHSO₂-aryl-R₁₇, -NHSO₂C₁₋₄alkyl, -SO₂NHR₁₇, -CONHR₁₇, and -NHC(=O)NHR₁₇;

R₁₄ is hydrogen, alkyl, or aryl;

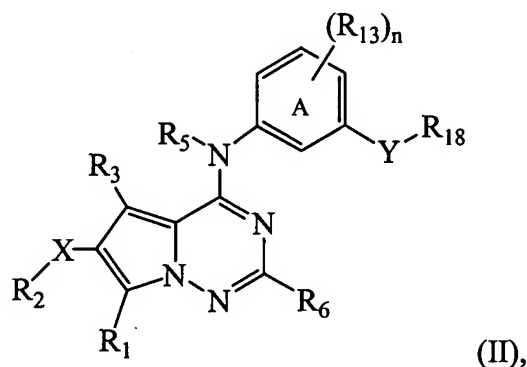
R₁₅ is hydrogen or alkyl;

R₁₆ is hydrogen, alkyl, aralkyl, or alkanoyl; and

R₁₇ is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl; and

n is 0, 1, 2 or 3.

5. (Currently Amended) The method of claim 3 comprising administering to the patient at least one compound having the formula (II):



or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R₃ is methyl or CF₃;

X is -C(=O)NR₁₀-, -NR₁₀C(=O)-, or -C(=O)-, ~~or~~ -CO₂-;

R₁ is hydrogen, -CH₃, -OH, -OCH₃, halogen, nitro, or cyano;

Y is -C(=O)NH-, -NHC(=O)NH-, -NHSO₂-, or -SO₂NH-;

R₁₀ is hydrogen or lower alkyl;

R₁₈ is selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with one to three R₁₉, except that when Y is -NHSO₂-, R₁₈ is C₁₋₄alkyl, aryl or aryl substituted with R₁₉;

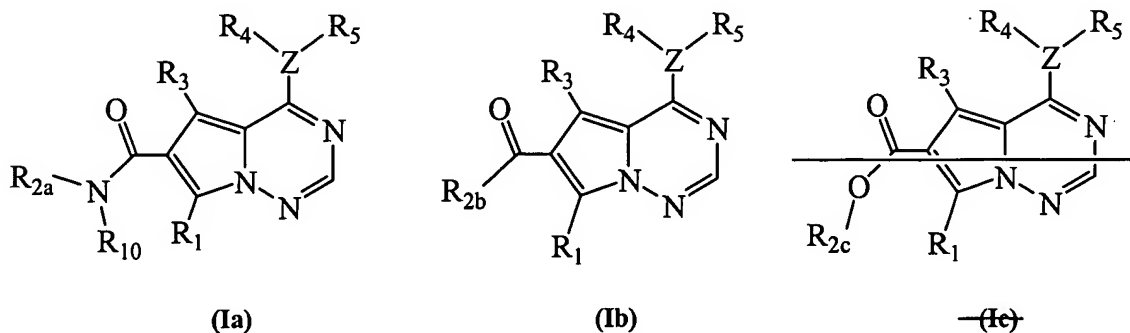
R₁₃ is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, -OR₁₄, -C(=O)alkyl, -OC(=O)alkyl, -NR₁₅R₁₆, -SR₁₅, -NO₂, -CN, -CO₂R₁₅, -CONH₂, -SO₃H, -S(=O)alkyl, -S(=O)aryl, -NHSO₂-aryl-R₁₇, -NHSO₂C₁₋₄alkyl, -SO₂NHR₁₇, -CONHR₁₇, and -NHC(=O)NHR₁₇;

R₁₄, R₁₅, R₁₆ and R₁₇ are hydrogen or alkyl;

R₁₉ at each occurrence is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each group R₁₉ may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl; and

n is 0, 1 or 2.

6. (Currently Amended) The method of claim 3, comprising administering to the patient at least one compound having the formula (Ia), (Ib), or (Ic):



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R₃ is methyl or CF₃;

R_{2a} and R_{2c} are independently selected from hydrogen, C₂₋₆alkyl, substituted C₁₋₄alkyl, aryl, substituted aryl, benzyl, and substituted benzyl;

R_{2b} is heterocyclo or substituted heterocycle; and

R₁₀ is hydrogen or lower alkyl.

7. (Original) The method according to claim 1 wherein the one or more conditions associated with p38 kinase are selected from inflammatory disorders.

8. (Original) The method of claim 7, in which the inflammatory disorder is selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, diabetes, inflammatory bowel disease, osteoporosis, psoriasis, graft vs. host rejection, atherosclerosis, and arthritis including rheumatoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis.

9-11. (Canceled)

specific inhibitors of the p38 MAPK's would empirically inhibit production of tumor necrosis factor (TNF)- α and interleukin (IL)-1 by lipopolysaccharide (LPS)-stimulated Cells. *Saklatvala* at 372. Hence, one skilled in the art would logically recognize that the presently claimed compounds would be expected to treat inflammatory-related diseases in general and the specific disorders discussed hereinbelow. In fact, Saklatvala states, "any inflammation strongly dependent upon the two primary cytokines (i.e., TNF- α and IL-1) will be reduced by p38 blockade." *Id.* at 376. Moreover, it is recognized that a "large body of evidence from preclinical studies indicates a crucial role of p38- α MAPK in inflammation." S. Kumar, et al., "p38 MAP Kinases: Key Signalling Molecules As Therapeutic Targets for Inflammatory Diseases," *Nature Reviews: Drug Discovery*, Vol. 2, Sept. 2003, 717-726, 722.

Not only has p38 inhibitor compounds been implicated in inflammatory disease in general, but such compounds, including the compounds taught in the instant invention, are known by those skilled in the art to be effective in treating the disorders identified in Claim 8.

TNF- α inhibitors are known to treat arthritis and psoriatic arthritis. P.J Mease, et al., "Psoriatic Arthritis Treatment: Biological Response Modifiers," *Ann. Rheum. Dis.*, 2005, 64 (Suppl. II), ii78-ii82; and S. Kumar, et al. at 725. TNF- α inhibitors have been shown to reduce symptoms and signs of ankylosing spondylitis as well as improve the patients' quality of life while reducing serious toxicities. J.C. Davis, Jr., "Understanding the Role of Tumor Necrosis Factor Inhibition in Ankylosing Spondylitis," *Seminars in Arthritis and Rheumatism*, 34:668-677 (2004).

The TNF- α inhibitors Etanercept, Infliximab and Adalimumab, among others, have been shown to be effective in clinical trials to treat psoriasis patients. K.A. Papp, "The Long-term Efficacy and Safety of new Biological Therapies for Psoriasis," *Arch Dermatol. Res.*, 298: 7-15 (2006); and Mease, et al., at ii78, ii81. It is also known to one skilled in the art that TNF- α plays a pivotal role in psoriasis and that p38 is activated in lesional psoriatic skin. C. Johansen, et al., "Protein Expression of TNF- α in Psoriatic Skin is Regulated at a posttranscriptional Level by MAPK-Activated Protein Kinase 2," *The Journal of Immunology*, 176, 1431-1438, 1431 (2006); and C. Johansen, et al., "The Mitogen-Activated Protein Kinase p38 and ERK $\frac{1}{2}$ are Increased in Lesional Skin," *Brit. Journal of Dermatology*, 152, 37-42 (2005).